REVIEW ARTICLE

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Comparative Effectiveness of Intratympanic Corticosteroids Versus Antibiotics in the Treatment of Meniere's Disease: A Review Study

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Abstract

Meniere's disease is an inner ear pathology characterized by recurrent episodes of vertigo, sensorineural hearing loss, a sensation of fullness in the ear, and tinnitus. It is estimated to occur at a rate of 15 individuals per 100,000 globally. Several recommendations exist for treating the disease, but there is no exact guideline to approach its management. In this study, we reviewed a decade of studies on the intratympanic approach to treating Meniere's disease which compared corticosteroids and antibiotics used on the condition. We found that the available data present conflicting evidence, and studies that investigated intratympanic gentamicin or dexamethasone did not demonstrate conclusive improvement in patient outcomes.

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Introduction

Meniere's disease is an internal otic disorder marked by the following triad of symptoms: hearing loss, episodes of vertigo, and tinnitus. Typically, the disease progresses gradually and can profoundly affect the overall quality of life of patients (1). The incidence of Meniere's disease ranges from 3.5 to 513 cases per 100,000 individuals, with a higher occurrence noted among older and white female patients (2, 3).

The exact underlying pathophysiology of Meniere's disease remains unknown. However, the most frequently observed histological alteration is as endolymphatic hydrops, which does not occur uniformly in all individuals diagnosed with the condition. Endolymphatic hydrops refer to the increased volume in the endolymphatic compartments and the subsequent distension of Reissner's membrane. Similarly, the precise etiology of endolymphatic hydrops is not fully understood, although current hypotheses suggest that it may result from an imbalance in the absorption and production of endolymph within the cochlea (4). Various available treatment modalities for Meniere's disease, exhibit considerable differences in different countries. However, none have successfully provided a definitive treatment for the condition. Given that many treatments can considerably affect the functionality of adjacent structures, it is advisable to initiate management with non-invasive strategies to minimize potential side effects before utilizing more invasive interventions (5-8).

The most common treatments prescribed for the disease are intratympanic steroid or gentamicin

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injections. Studies suggest that intratympanic steroid injections can potentially decrease the frequency of vertigo episodes, without interfering with auditory capabilities. In contrast, intratympanic gentamicin injections exhibit potent ablative effects on vestibular cells. However, the administration of gentamicin is associated with adverse effects, notably sensorineural hearing loss, due to its inherent toxic effect on the cochlear cells (7, 8). Since there are no exact data about the treatment of Menier disease, this study aimed to review the effects of intratympanic corticosteroids or antibiotics on this condition.

Methods

In this review, the effect of intratympanic corticosteroids versus antibiotics on Meniere disease was investigated. Studies from 2014 to 2024 were searched in PubMed databases with the keywords “Ménière disease” AND/OR “intratympanic” AND/OR “corticosteroid” AND/OR “antibiotic”. Review articles, systematic reviews, meta-analysis, and editorials were excluded from the study. Also, studies the full text of which was not in English or unavailable were excluded from this review. Initially, 161 studies were found with the mentioned keywords; of which, 71 were in the desired duration. Of these 71 studies, 9 studies met the inclusion criteria, and 68 studies were excluded from this review, given their design (systematic review, review articles, etc.) or language.

Results

Intratympanic corticosteroids

Lambert et al. (9), investigated the effect of intratympanic dexamethasone compared to a control group. 157 patients (77 in each group) participated in the study. Administration of one intratympanic unit of OTO-104 during 3 months significantly reduced vertigo compared to the baseline. OTO-104 is a dexamethasone suspension in a buffer solution containing a thermally reversible glycol Poloxamer 407 (10). This compound contains 12 mg of dexamethasone (9). In the 2nd and 3rd months, the changes between the treatment group and the placebo were significant. The number of vertigo episodes in the treatment group was significantly lower than in the placebo group. On the other hand, vertigo severity scores were significantly lower in the group that received OTO-104 (14% absolute reduction and a 44–56% relative reduction). In the OTO-104 group, the average daily vertigo attacks were significantly lower in the second month (from 1.91 at baseline to 0.62). A 22% reduction in the number of daily vertigos in the OTO-104 group was not significantly different from the placebo in the third month. For both OTO-104 and placebo groups, tinnitus frequency, changes from the baseline in tinnitus frequency, mean tinnitus intensity degree and THI-25 (tinnitus handicap inventory) were stable during the follow-ups and equal in the two groups (9).

Albu et al. (11), studied how well intratympanic dexamethasone worked compared to high-dose betahistine in severe unilateral Meniere disease management. They randomly assigned 66 patients with confirmed unilateral Meniere disease into two groups (group A: intratympanic dexamethasone along with placebo tablets, group B: high-dose betahistine (max dose: 144 mg/day) and intratympanic saline). The injections were given three times, spaced 3 days apart. They measured vertigo control, tinnitus questionnaire, speech discrimination score, pure tone average (PTA), vertigo questionnaire, and functional level score. They demonstrated that there were no significant differences between high-dose betahistine and intratympanic dexamethasone on PTA, speech discrimination score, vertigo control, functional level score, and tinnitus.

The aim of Molnar et al.'s study (12), was to follow up on the effects of intratympanic steroid treatment on hearing loss in MD. They administered 4 mg/ml dexamethasone for 105

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previously diagnosed MD patients. In 68.6% of cases, the administration of intratympanic dexamethasone resulted in a stabilization of the hearing loss and halting the progression of the hearing loss. A significant relationship was observed between the administration of dexamethasone and the improvement of hearing loss. They concluded that intratympanic dexamethasone can prevent the hearing loss progression in patients with MD.

Al Attrache et al. assessed the effectiveness of intratympanic dexamethasone injection in 24 MD patients who had not improved with the first line of treatments. In this case-control study, patients received 3 separate intratympanic dexamethasone injection (16 mg/ml) weekly and were matched with 24 control participants. The case and control groups had no significant differences in vertigo spells. The authors concluded that intratympanic administration of dexamethasone does not eliminate the likelihood of experiencing vertigo spells in the future.

Phillips et al. (14), evaluated the intratympanic effect of OTO-104. Patients received an intratympanic injection of 12 mg OTO-104 or placebo (1:1) and were followed up for 3 months. This study was conducted in three phases known as AVERTS. OTO-104 had a greater reduction in definitive vertigo days (DVD) than placebo. One phase of the study (AVERTS-2, n = 174, p = 0.029) showed significant vertigo control at month 3 in terms of vertigo impact on daily activity (days at home or in bed), vertigo severity, and vertigo frequency. In the AVERTS-1 phase, OTO-104 group the mean DVD experience was significantly lower in month 3 of the follow-up. It should be mentioned that the placebo response was considerable in all phases of Meniere's disease.

Beyea et al.'s study (15), evaluated the efficacy of different protocols of dexamethasone intratympanically injection (IT Dex) to treat intractable unilateral Meniere's disease. 106 definitive unilateral Meniere's disease with no response to first-line management were evaluated. Patients were selected based on the absence of prior oral steroids, IT steroids, or ablative therapy in their past medical history. A single injection followed by 4 injections was planned. The authors found that PTA scores significantly dropped after treatment and there was no significant difference between the outcome of the treatment between the two protocols.

Pradhan et al. (16), evaluated intratympanic dexamethasone effects on intractable Meniere's disease in the long term. Thirty patients with refractory Meniere's disease, who exhibited no improvement with conventional medical management, underwent treatment with intratympanic dexamethasone injections. The outcomes related to hearing and dizziness were assessed post-treatment and compared to the values recorded before the intervention. The average score on the Dizziness Handicap Inventory (DHI) decreased significantly from 91.58 to 31.00 (p = 0.00) after three months of treatment. Subsequent follow-up assessments revealed mean DHI scores of 51.50, 46.6, and 50.90 at the follow-ups in six, twelve, and twenty-four months, respectively (p = 0.04). Notably, at the end of the twenty-four-month period, 23.80% of the patients reported being free from vertigo (p = 0.01). Throughout all follow-up intervals, no patients exhibited an improvement in hearing greater than 10 dB, while 6.6% experienced a decline in hearing.

Intratympanic antibiotic

Scarpa et al. (17), studied low-dose intratympanic gentamicin on reducing vertigo attacks in Meniere's disease. The treatment was prescribed for recurrent vertigo episodes. Forty-eight unilateral intractable Meniere's disease patients were assessed. 0.5 mL of 10 mg gentamicin with a dose of 80 mg/2 mL was administered for all patients at 2-week intervals. Vertigo attacks were assessed before and after treatment. Hearing and vestibular

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evaluation were done with video head impulse test (vHIT), vestibular, and pure tone audiometry. In the six months following treatment, the mean frequency of attacks per month had reduced to 0.52 ($p < 0.0001$). A total of thirty-four patients (70.8%) achieved Class A vertigo control, while thirty-seven patients (77%) attained either Class A or Class B. Additionally, five patients (10.4%) were classified in Class C or Class D, with no patients falling into Class E or F. The vestibulo-ocular reflex (VOR) gain was recorded at 0.9750 ± 0.2893 prior to treatment and decreased to 0.6857 ± 0.02742 post-treatment ($p < 0.0001$). Furthermore, there were no significant changes in the average PTA and the mean DHI scores before and after the treatment.

Bremer et al. (18), investigated intratympanic gentamicin effects in patients with Meniere's disease in a double-blinded placebo-controlled randomized controlled trial. Group 1 received 4 placebo injections with sterile NaCl 0.9% solution, group 2 received two injections with 40mg/mL gentamicin and two placebo injections in random orders, and group 3 received four 40mg/mL gentamicin injections, and were followed up for 2 years. The mean pre-treatment DHI score was 54 points, 44 points, and 46 points for the placebo group, gentamicin-placebo group, and gentamicin group, respectively. The mean DHI score for the placebo group was 24 points (decrease of 20 points), for the gentamicin-placebo group was 34 points (decrease of 10 points), and for the gentamicin group was 5 points (decrease of 41 points), and the latter group had the greatest decrease in scores. These changes were not statistically significant ($P>0.5$).

Sam et al. (19), investigated the effectiveness of intratympanic gentamicin on high and low-frequency hearing loss in unilateral definitive Meniere's disease. Intratympanic gentamicin patients were evaluated for tinnitus, vertigo, speech discrimination score, and mean pure tone audiometric. Follow-up was done up to 2 years. They found that the frequency of spells per month exhibited a significant reduction of 93.2% ($p = 0.005$) following the initial treatment. Prior to the intervention, eight participants reported experiencing tinnitus, whereas none reported this symptom post-treatment. Additionally, a follow-up assessment revealed an increase in hearing loss of 7.2 dB (+12%; $p = 0.027$). Notably, the hearing loss in the low-frequency spectrum demonstrated a substantial increase of 13.3 dB (+29%; $p = 0.027$). Conversely, the mean PTA threshold in the high-frequency range did not show a statistically significant change. Among the three participants who underwent two intratympanic gentamicin injections, the mean PTA threshold for the affected ear was recorded at 61.0 ± 11.5 dB prior to the second injection and 63.3 ± 15.3 dB after the subsequent injection. A clinically significant change in the speech discrimination score was observed in 50% of the participants during the follow-up period. The average shift in the speech discrimination score was recorded at 20.0 ± 17.3 dB ($p = 0.018$). It is noteworthy that the speech discrimination score was not assessed following a second intratympanic gentamicin injection.

Discussion

A range of interventions has been suggested for the management of Ménière's disease. These approaches encompass modifications in diet and lifestyle, oral medications, intratympanic injections, and surgical options. Aminoglycosides are delivered into the middle ear through the tympanic membrane, with significant variability in dosage and frequency of administration. Various treatment regimens have been employed, including three doses per day over several consecutive days or one to two doses spaced a month apart (20, 21).

Currently, there is no consensus on the optimal treatment for Ménière's disease, resulting in the absence of a definitive 'gold standard' to provide a basis for the comparison of other

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therapies. Aminoglycoside antibiotics can lead to adverse effects on balance and hearing by damaging the hair cells within the inner ear. This mechanism is intentionally utilized in the treatment of Ménière's disease to induce a functional imbalance of the affected ear, allowing the brain to adapt to the resulting unilateral vestibular hypofunction, provided that the contralateral ear maintains adequate function, thus making up for the loss of the other ear. The therapeutic goal is to selectively induce imbalance in the affected ear while striving to preserve hearing. Although all aminoglycosides impact the inner ear, gentamicin and streptomycin are noted for their predominantly vestibulotoxic effects, making them more commonly used in the context of Ménière's disease. Nonetheless, some individuals may exhibit susceptibility to the ototoxic effects of aminoglycosides (22-25).

Based on what we found, the most common type of corticosteroid for the management of Ménière's disease is dexamethasone and the most common antibiotic is gentamicin. It seems that gentamicin has better effects on the management of the disease than dexamethasone. The results of the studies that were conducted using gentamicin demonstrated significant effects on the outcomes of patients, but many studies on dexamethasone did not show significant effects.

Sam et al. (19) and Scarpa et al. (17), demonstrated significant effects of intratympanic gentamicin on Ménière's disease-related parameters including negative effects on hearing loss, positive effects on speech discrimination, and PTA threshold (only in the Sam et al.'s study (19), and the frequency of attacks/month and VOR gain (only in Scarpa et al.'s study(17).

It should be noted that Scarpa et al. did not find any differences before and after treatment in PTA and DHI scores. Also, Bremer et al. (18), did not find any changes in the DHI score after the administration of intratympanic gentamicin.

Gentamicin is classified as an aminoglycoside antibiotic. It demonstrates bactericidal properties specifically against aerobic gram-negative bacteria, thereby rendering gentamicin an effective choice for the treatment of various prevalent infections (26). Gentamicin is an ototoxic antibiotic exhibiting a greater tendency to affect the vestibular system compared to the cochlea. Its ototoxic effects are contingent upon the dosage administered. When given at the correct dosage, gentamicin can alleviate symptoms of vertigo while preserving the integrity of the vestibular and cochlear sensory neuroepithelium (27, 28).

More studies were performed for evaluation of the effects of dexamethasone on Ménière's disease than gentamicin. The findings of the studies are quite controversial. Lambert et al. (9), found that vertigo and its severity decreased after the administration of intratympanic dexamethasone in the patients, but THI and tinnitus were not change after the administration. Molnar et al.'s study (12) found a significant relationship between the administration of dexamethasone and the improvement of hearing loss. Pradhan et al. (16) found that DHI scores decreased significantly after three months of treatment with intratympanic dexamethasone. Vertigo was significantly reduced and hearing loss was improved after the treatment.

In contrast, Al Attrache et al (13), mentioned that intratympanic administration of dexamethasone does not eliminate the likelihood of experiencing vertigo spells in the future. Albu et al. (11), found that there were no significant differences between high doses of betahistine and intratympanic dexamethasone in vertigo control, PTA, speech discrimination score, functional level score, vertigo, and tinnitus. Corticosteroids represent an alternative approach in the treatment of intratympanic injections. These medications can be introduced into the middle ear through the tympanic membrane. While injections are the most common method of administration,

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they may also be delivered as drops via a ventilation tube, with or without the use of a wick. Treatment protocols can range from a single injection to a brief series of two to three injections, with the possibility of repetition if symptoms reappear. Various corticosteroids may be utilized, such as methylprednisolone, dexamethasone, or hydrocortisone. However, despite thorough investigation, no studies had examined other corticosteroids than dexamethasone, as all reviewed studies focused exclusively on this particular agent (29-32).

Phillips et al. (14), mentioned that dexamethasone injections significantly decreased the mean DVD in month 3 after the injection compared to placebo. It was notable that a significant placebo response was observed in all phases of the study in patients with Meniere's disease. It was controversial as this study argued that tymapnic manipulation might improve the symptoms, rather than the injected agent. On the other hand, Beyea et al.'s study (15), found that PTA scores significantly worsened after treatment with dexamethasone and there was no significant difference between the outcome of the treatment with the protocol administration. This shows that dexamethasone should be carefully administered.

Autoimmune context is considered as the main etiology of Ménière's disease providing the basis with which dexamethasone prescriptions were justified. However, the cumulative conclusions of studies done on the subject beg to differ (33, 34).

Conclusion

Given the lack of an exact treatment method for Ménière's disease and the controversial available data without a definitive conclusion on the effectiveness of gentamicin or dexamethasone, more studies are required with alternative agents or therapies as the treatment options for Ménière's disease.

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Conflicts of Interest

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